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EDITORIAL

Corticosteroids in sepsis: certainties and shadows

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When Hench and colleagues first described the effects of corticosteroids [1], they surely have not anticipated that in the third decade of the third millennium, these drugs would be the most prescribed anti-inflammatory agents worldwide. Nearly 3% of the world population are exposed to corticosteroid therapy [2], and the mainstay of rheumatoid arthritis treatment [3]. And yet, corticosteroid therapy in sepsis remains the most controversial topic even after more than 80 trials accounting and 22,000 participants [4]. This narrative concise review aims to guide the reader through what is certain and uncertain about the use of corticosteroids in sepsis.

How corticosteroids work?

The mechanisms of action of corticosteroids gained clarity with advances in molecular biology, which confirmed their pleiotropic and cell-specific action through both genomic and non-genomic effects [3]. Corticosteroids modulate the interaction between stroma cells, resident macrophages and blood-borne immune cells at all steps of the inflammation [5]. Then, a breach to the epithelium caused by an invading microorganisms triggers, within minutes, pathogen-/damage-associated molecular patterns (PAMPs/DAMPs) activation of resident macrophages with release of proinflammatory mediators (e.g., histamine, chemokines). The second step occurs in the following hours with recruitment of blood-borne immune cells, increased pathogens killing activities of these cells. After a few days and tissues freed from living pathogens, corticosteroids reprogram resident macrophages toward type 2 (anti-inflammatory) macrophages to fine-tune the clearance of all debris (from pathogens and body cells). Subsequently, the repair phase of the inflammatory process begins, during which corticosteroids modulate growth factors release, collagen synthesis and reepithelization. Regulation of mitochondrial metabolic flux is also essential to the anti-inflammatory effects of corticosteroids [3]. The effects of corticosteroids on the metabolism of immune cells are mostly mediated by non-genomic interactions between glucocorticoid receptor (GR) and pyruvate dehydrogenase, which are crucial for the organism's immediate immune response. Despite these advanced features, many unanswered questions remain such as how to explain the cell-specific effects of corticosteroids, and what is the functional relevance of the tetrameric isoform of the GR (Fig. 1).

From bench to bedside

In both preclinical and clinical sepsis settings, the effect of corticosteroids on biological systems is established.

Clinical relevance of corticosteroids for organ dysfunction

Corticosteroids enhance vasomotor tone synergistically with catecholamines [6], reducing vasopressor dependency in patients with septic shock. A recent systematic review and meta-analysis found that compared to placebo or usual care, corticosteroids probably increase the chance of having shock reversed on day 7 (18 trials; 6938 participants; RR 1.22 (95% CI 1.13 to 1.33; $P<0.00001$; random effects model) [4]. However, the relative contributions of the GR and MR signaling still remain unclear [6]. While corticosteroids prevented the onset of vasopressor dependency in patients with severe community acquired pneumonia (CAP), [7] they did not in septic patients with other triggering infections [8]. Corticosteroids rapidly suppressed the expression of nuclear-factor

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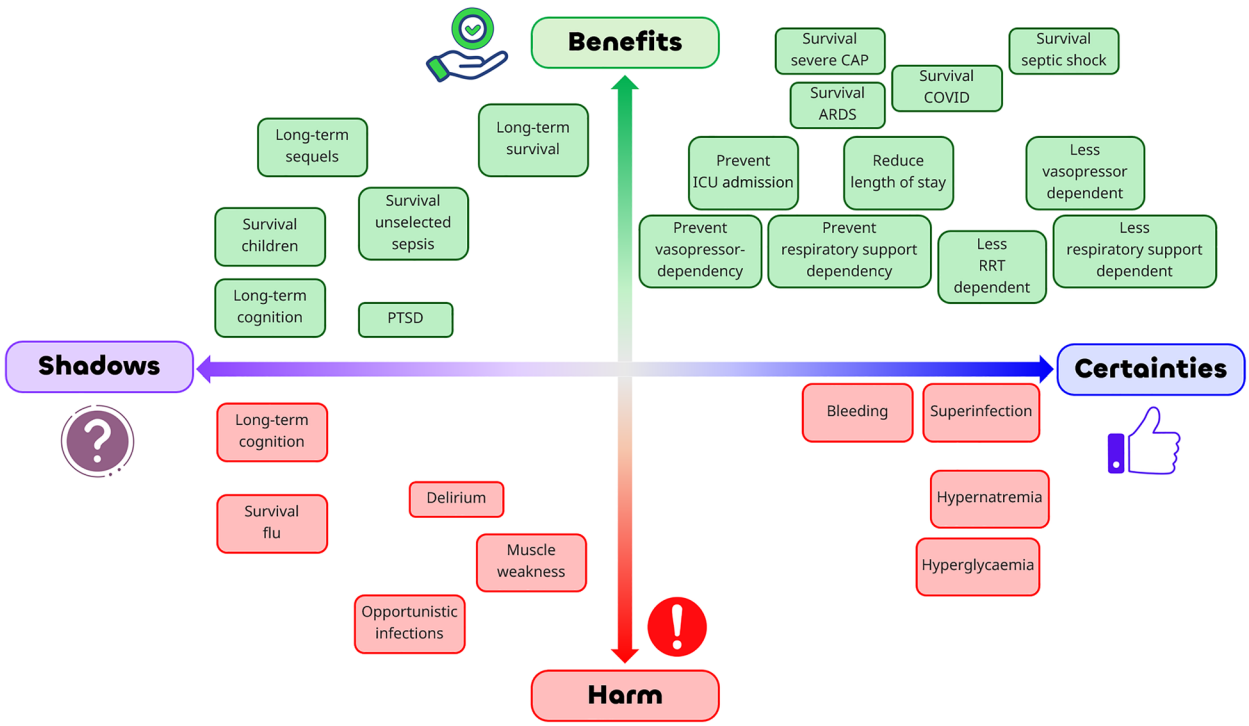

Fig. 1 Summary of potential benefit and harm from corticosteroids. Potential benefits and harms from corticosteroids. The figure summarizes the certainties and shadows on the benefit and harm of corticosteroids in sepsis. Arrows indicate direction to the strongest effects (whether benefit or harm) and to certainty or uncertainty of evidence. *PTSD* Post-traumatic stress disorders; *RRT* Renal replacement therapy

kB in septic shock [9], and the downstream release of proinflammatory mediators without causing immunosuppression [10]. In line with these biological immune effects, compared to placebo or usual care, corticosteroids reduced the severity and number of organ's dysfunctions as measured by the SOFA score on day 7 (17 trials, $n=3220$ participants) mean difference (MD) −1.27 (95% CI −1.63 to −0.92; $P<0.00001$; random effects model) [4]. As a result of accelerating the recovery of organ function, corticosteroids may reduce length of stay in the ICU (25 trials, $n=8069$, MD −0.86 days (95% CI −1.67 to −0.05; $P=0.04$; random effects model) and in the hospital ($n=31$ trials, $n=16{,}954$ participants, MD −1.09 days (95% CI −1.85 to −0.34; $P=0.005$; random effects model) [4]. While the benefits of corticosteroids on the cardiovascular and respiratory systems are well studied, data are insufficient to inform physicians on their effects on sepsis-induced dysfunction in other organs, such as kidneys, liver, or brain.

Glucocorticoids and clinical outcomes

The latest comprehensive trial-level meta-analysis found that, in sepsis, compared to placebo or usual care, corticosteroids probably reduced 28-day mortality (72 trials, $n=22{,}915$, RR: 0.89 (95% confidence interval [CI] 0.84 to 0.95; $P=0.0007$; random effects model) [4]. Treatment effects on 28-day mortality were not modified by the type or the mode of administration (bolus versus continuous) of corticosteroids, and were of greater magnitude when corticosteroids were given at lower initial and cumulated doses and for a longer duration. While age and severity of illness were not modifiers of corticosteroids effects, this meta-analysis found that corticosteroids reduced 28-day mortality when sepsis was related to CAP or complicated by ARDS or shock and not in patients with uncomplicated sepsis (test for subgroup differences: $Chi^2=16.05$, $df=4$ ($P=0.003$), $I^2=75.1\%$) [4]. These findings are in line with most recent meta-analysis investigating corticosteroid therapy for CAP [11]. Corticosteroids did not increase the risk of complications and sequels, i.e., digestive bleeding, secondary infections, neurological sequels, except transient hyperglycemia and hypernatremia [4].

Unanswered questions about glucocorticoids

There are several gaps in the evidence. First, there is insufficient information for robust conclusion about the effects of corticosteroids in children with sepsis, and about their long-term effects on survival and sequels in adults. Second, it remains uncertain whether survival benefits from corticosteroids are source-specific, i.e.,

respiratory sepsis versus others [4]. Third, the added value of fludrocortisone as an add-on treatment to hydrocortisone is still controversial [12]. Fourth, the benefit-to-harm ratio of corticosteroids in viral sepsis other than critical COVID-19 warrants to be investigated in adequately powered trials. Fifth, genetic, genomic and non-genomic factors likely influence clinical response to corticosteroids and most of them remain to be discovered [3].

From evidence-based guidelines to bedside practice

Most recent guidelines suggested administering corticosteroids to adult patients with septic shock (low certainty of evidence), and to those with ARDS (moderate certainty of evidence) and recommended administering corticosteroids to adults with severe bacterial CAP (moderate certainty of evidence) [12]. A survey of 542 US critical care physicians found that 83% do not routinely use corticosteroids in adults with sepsis, contrasting with 81% reporting common use of corticosteroids for septic shock [13]. Roughly, one out of three respondents to the survey believed that corticosteroids reduce mortality in septic shock, whereas 27% did not and 45% were unsure. Hydrocortisone was the most common corticosteroid prescribed (93%), with a median dosage of 200 mg/d and administration via intravenous boluses. A retrospective multicenter study ($n=4198$ patients) reported that routine implementation of hydrocortisone therapy was associated with a global reduction in septic shock-related 90-day mortality (14% vs. 24% absolute difference, adjusted HR for hydrocortisone effect −0.81; 95% CI 0.65–0.99; $p=0.044$) in Australia [14]. Another retrospective comparative cohort analysis of routinely collected data in the USA showed that the implementation of fludrocortisone added to hydrocortisone resulted in an additional 3.7% reduction in hospital mortality or hospice discharge [15].

Despite decades of research, there is still insufficient information on the routine practices for the use of corticosteroids in sepsis and on their global health and socioeconomic impact.

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Declarations

Conflicts of interest
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